REMARKS

Claims 1-3, 7-17 and 25-44 were pending. Applicants have canceled claim 43 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application. Accordingly, no new matter is introduced by these amendments and entry of the amendments to the record is requested. Claims 1-3, 7-17, 25-42 and 44 are pending and under consideration.

35 U.S.C. § 112, first and second paragraphs

Claim 43 is rejected under 35 U.S.C. § 112, first and second paragraphs as failing to comply with the written description requirement and as being indefinite. Without acquiescing to these rejections, and solely in the interest of advancing prosecution, Applicants have canceled claim 43, rendering this rejection moot.

Withdrawal of previously pending 35 U.S.C. § 103(a) rejections

Applicants note that although the previously pending rejections of the claims under 35 U.S.C. § 103(a) are not repeated, the Office has not stated that they are withdrawn. Applicants respectfully request that the Office state for the record that these rejections are withdrawn.

35 U.S.C. § 103(a) – Obviousness

Claims 1-3, 7-17 and 25-44 are rejected under 35 U.S.C. § 103(a) as obvious over Gewirtz et al., in view of Patel et al., Sachetto et al., Yacyshyn et al. and Bennett et al. (US 6,096,722). Based on these references, the Office concludes that it would have been obvious "to use alicaforsen… in an enema formulation to rectally administer alicaforsen into a human patient having pouchitis." *Office Action* at page 8. It is asserted that one of skill in the art would be motivated to do so because: 1) the Office assert that Gewritz discloses that alicaforsen can reasonably be expected to treat IBD that shows an increase in ICAM-1; 2) Patel allegedly discloses that ICAM-1 is suggested to be a useful target for treating pouchitis and ulcerative colitis (UC), that ICAM-1 levels are elevated in pouchitis, and that the clinical aspects of pouchitis are tightly associated with those of UC; 3.) Sachetto is purported to disclose the

interchangeability of HPMC in an enema for pouchitis and UC; 4.) an enema formulation comprising alicaforsen with a penetration enhancer such as HPMC is taught by Bennett et al.; and, 5.) evaluating the dosage, schedule, and frequency of administration is allegedly within the skill in the art based on Yacyshyn. *Id.* at page 8-11. Applicants respectfully traverse.

As an initial matter, Applicants submit that the Office has misstated or misrepresented the teachings of several of the cited references.

First, the Office emphasizes the statement in Gewirtz that reduction of ICAM-1 by alicaforsen "can reasonably be expected to be therapeutic for [IBD]." However, this statement at the beginning of the article laying out the rationale for use of alicaforsen in treating Crohn's disease (CD) and UC is in contrast to the remainder of the article. Read in its entirety, Gewirtz does not support the Office's assertion about what was a "reasonable" expectation.

Gewirtz states that the initial phase III trials of alicaforsen for CD were a failure. *Gewirtz* at Abstract. According to Gewirtz, two phase II trials of alicaforsen for CD produced mixed results – one study found the drug "considerably effective," while the other "did not show a significant effect." *Id.* at page 1402, col. 2, final paragraph. Applicants note that in at least the successful study, alicaforsen was administered by intravenous infusion, not as an enema. *See Exhibit 1* (previously submitted). Finally, Gewirtz states that a new phase III trial for CD was underway, but no results are provided. As for treatment of UC, Gewirtz discloses that in December 1999, an enema formulation of alicaforsen entered phase IIa trials, "[h]owever, no further data are available." *Id.* at page 1402, col. 2, 3rd full paragraph. Clearly, as phase IIa clinical trials are the first clinical trials run to obtain preliminary data on the effectiveness of a drug, the clinical utility of alicaforsen in enema formulation for treating UC was not yet known.

Gewirtz et al.'s statements at the conclusion of the article are more relevant for determining whether it was reasonable to conclude that alicaforsen could treat UC or CD:

> Whether alicaforsen can reduce ICAM-1 expression in humans to an extent significant enough to be therapeutic in CD, at drug concentrations that do not cause unacceptable side effects, has yet to be determined.
>
> While the overall available data suggest the drug has some therapeutic benefit toward this disorder, additional clinical trials are necessary before any **reasonable** assessment of its value can be made. ... If safe doses with efficacy levels approaching the wonderful response seen in the first double-blind placebo-controlled trial can be established, alicaforsen would be widely used in CD. Alicaforsen could be especially useful for reducing the steroid dependence of

> Crohn's disease patients as long-term steroid use is associated with many problems. Should effective subcutaneous or enema dosing be established, alicaforsen would be considerably more desirable. For now, antisense therapeutics such as alicaforsen remain a promising but unproven therapeutic strategy. While it seems likely that antisense drugs will eventually be clinically useful, whether it will be phosphorothioates or a later generation of antisense molecules that achieve significant clinical utility remains to be seen. *Gewirtz* at page 1403, col. 2 (emphasis added).

Gewirtz et al.'s statements indicate that the therapeutic value of alicaforsen was promising, but unproven and unknown, and that additional clinical trials were necessary "before any reasonable assessment of its value" could be made. Based on Gewirtz, one of skill in the art would conclude that additional studies were needed before there could be any reasonable expectation of success in treating Crohn's Disease using alicaforsen. If more data are needed before the value of alicaforsen for treating CD can reasonably be determined, then one of skill in the art would have to conclude that the value of alicaforsen for treating pouchitis is even less certain, and there is no reasonable expectation of success.

Second, the Examiner asserts that "Patel et al. teach that pouchitis, Crohn's disease, and ulcerative colitis are classified as chronic inflammatory bowel disease (IBD)..." *Office Action* at page 6. Applicants respectfully submit that Patel does not state that pouchitis is a form of IBD.

In fact, throughout Patel, the authors refer to "inflammatory bowel disease and pouchitis," keeping the two terms distinct. *See, e.g., Patel* at Abstract; page 1040, second column. Applicants are not aware of any portion of Patel where pouchitis is classified as a form of IBD.

Third, the Office states that Sachetto et al. "teach that the pouchitis treatment method is also useful in treating patients having ulcerative colitis or Crohn's disease." *Office Action* at page 7.

Applicants note that Sachetto includes only a single working example which describes treating pouchitis with a xanthum gum enema formulation. Sachetto does not provide any data regarding the use of the disclosed enema formulations to treat UC or CD. While Sachetto asserts that the treatment would work for these diseases, the actual data disclosed in Sachetto does not support the assertion that treatments for UC and pouchitis are interchangeable.

Fourth, the Office asserts that Yacyshyn et al. teach doses of alicaforsen for treating CD and concludes that based on the pharmacokinetics of alicaforsen in the CD study, "evaluating and

determining doses, administration frequency, and administration duration" for any disease is within the technical grasp of one of ordinary skill in the art. *Office Action* at page 7.

Applicants note that while alicaforsen showed some promise for treating CD, the compound was administered by intravenous infusion, not by enema. Additionally, as discussed below, CD and pouchitis are distinct diseases with distinct therapies. Thus, Yacyshin does not support the assertion that an alicaforsen treatment for CD can lead to an alicaforsen treatment for any disease much less pouchitis.

Fifth, the Office asserts that Bennett discloses "that ISIS 2302 has been evaluated up to Phase II trials for patients with Crohn's disease and ulcerative colitis, where in said ISIS 2302 has consistently demonstrated desired therapeutic efficacy. See Examples 51-55." *Office Action* at page 8.

Applicants note that the cited portion of Bennett, Examples 51-55, report that clinical trials on ISIS 2302 are underway, but there are no therapeutic results reported for Examples 51, 53, 54, and 55. While there are therapeutic results reported for Example 52, where ISIS 2302 shows promising results for the treatment of CD, the compound was administered intravenously, not by enema. Thus, Bennett does not report any therapeutic results on the use of ISIS 2302 as an enema for the treatment of any humans.

Applicants' turn next to the Office's conclusion that the pending claims are obvious in view of the cited references. The Office's argument essentially amounts to the assertion that because it is reasonable to investigate alicaforsen for the treatment of UC and CD based on elevated levels of ICAM-1 in these diseases, and it is known that ICAM-1 is elevated in pouchitis (Patel), one of skill in the art would be motivated to treat pouchitis with alicaforsen. In addition, based on Sachetto, the interchangeability of treatment for pouchitis and UC using an enema was known, Bennett teaches that enama formulations of alicafosen are "efficacious," and details regarding dosing are within the skill in the art (Gewirtz; Yacyshin).

Applicants respectfully submit that several points of this argument are not supported by the evidence of record.

First, as noted above, Gewirtz states that "additional clinical trials are necessary before any **reasonable** assessment of its value can be made." Thus, the Office's first point on page 8 of the Office Action is not supported by the totality of the Gewirtz reference.

Second, the Office's arguments rest on the assertion that the efficacy of enema formulations of alicaforsen for CD has been established, and that any enema treatment for UC or CD will be successful in treating pouchitis, merely because the diseases have similar symptoms, and ICAM-1 is elevated in all three diseases. This assumption is not supported by the evidence.

Applicants note that none of the cited references, nor any combination of references, support the assertion that the efficacy of enema formulations of alicaforsen has been established. Contrary to any assertions by the Office, Bennett does not report any therapeutic results on the use of ISIS 2302 as an enema for the treatment of any humans.

There is also no reason to assume that all diseases having elevated ICAM-1 can be treated with alicaforsen. As Patel et al. note, "[r]aised levels of soluble forms of these intracellular cell adhesion molecules, namely sICAM-1, sE-Selectin and sVCAM-1, have been found in the plasma of a variety of disease states including chronic inflammatory liver disease, diabetes, some carcinomas, allograft rejection and systemic vasculitides." *Patel* at page 1037, col. 2 (citations omitted). One of skill in the art would not expect inhibition of ICAM-1 to treat all of these various diseases – from cancer to diabetes – simply because they share elevated cell adhesion molecule levels.

Finally, contrary to the Office's assertions, CD, UC and pouchitis are distinct diseases and their treatments are not interchangeable.

Some patients with UC or familial polyposis may undergo surgery to form an ileal pouch (Example 17 of the instant specification) and sometimes the pouch will develop pouchitis. The fact that UC and pouchitis share some symptoms does not provide a basis for assuming that treatment successful for one will be successful for the other. For example, Kornbluth et al. disclose that the clinical practice guidelines for treating UC involve the administration of anti-inflammatory compounds, steroids and immune-suppressants. *See Kornbluth* at page 1373, col. 1, 1st full paragraph; page 1374, col. 1, first full paragraph; 1376, col. 1, second full paragraph (previously submitted as Exhibit 2).

CD is a separate and distinct disease from pouchitis. CD is a systemic disease with inflammation often developing outside the colon such as the joints, eyes or skin. *See Mayo Clinic website*, 12/15/09 website download herein submitted as Exhibit 4). The Mayo Clinic guidelines for treating CD involve the administration of anti-inflammatory compounds and

immune-suppressants. Surgery to form the ileal pouch is usually contraindicated in patients with CD. *See Shen et al.*, at page 942, col. 2, 1st full paragraph (*Inflamm Bowel Dis*, 2008, 14(7):942-948, herein submitted as Exhibit 5). Although CD can develop in subjects with an ileal pouch, Shen makes clear that pouchitis and Crohn's disease of the pouch are separate and distinct diseases.

> "All patients with a confirmed diagnosis of CD of the pouch in the Pouchitis Clinic between 2002 and 2007 were evaluated. Patients with...pouchitis...were excluded." *Shen* at page 942, methods section.

Pouchitis is a local inflammation of the ileal reservoir (i.e. pouch). *See Mahadevan* at page 1646, summary (previously submitted as Exhibit 3). In contrast to UC and CD, pouchitis is primarily treated with antibiotics or probiotics. *See Mahadevan* at page 1640, col. 2, 2nd full paragraph. Thus, one of skill in the art would recognize that although CD, UC and pouchitis are similar in some respects, their standard treatments are different, and there is no expectation that what is successful in treating one will be successful in treating the other – otherwise the recommended standard treatments would be the same. None of the cited references demonstrate to the contrary, as Sachetto provides no evidence to support a claim of treating UC or CD with an enema that apparently treats pouchitis.

In sum, the cited references do not provide one of skill in the art with a reasonable basis to believe that enema formulations comprising an antisense oligonucleotide having the nucleobase sequence recited in SEQ ID NO: 1 can be used to successfully treat pouchitis. None of the references demonstrate successful treatment of CD, UC or pouchitis using enemas containing ICAM-1 antisense. In addition, similarities of symptoms between CD, UC and pouchitis do not translate into similar recommendations for standard treatments – they are in fact distinct diseases in spite of some shared symptoms. Therefore, even if *arguendo* enemas containing ISIS 2302 were successful in treating CD or UC, a fact the cited references have not established, there is no expectation that it would also work for treating pouchitis since they are distinct diseases.

Unexpected Results

Even if the Office has established a *prima facie* case of obviousness, a point Applicants do not concede, Applicants submit that the claimed methods have unexpected results that are sufficient to demonstrate nonobviousness.

The results reported in Example 17 of the instant specification demonstrate that treatment with an enema formulation of antisense targeting ICAM-1 resulted in remission of 58% of patients. A month after treatment ended, 50% of the patients were still in remission. This is particularly surprising because the patients being treated were suffering from chronic, unremitting pouchitis that was unresponsive to other therapies. *See Specification* at ¶ [0320]. Thus, Applicants have provided a successful treatment for a chronic disease that currently has no other therapy available – a treatment which is successful in over half the patients tested, and which maintains remission for at least a month after treatment ceases. None of the cited references provide a basis for expecting such a successful outcome.

Conclusion 35 U.S.C. § 103(a) rejections

None of the cited references, alone or in combination, provide a reasonable basis for one of skill in the art to expect that enema formulations comprising an antisense oligonucleotide having the nucleobase sequence recited in SEQ ID NO: 1 would successfully treat pouchitis. The Gewirtz reference states that additional data is needed before a reasonable assessment can be made of whether ISIS 2302 can successfully treat CD. Bennett does not report the successful treatment of any human disease using an enema formulation of ISIS 2302, and does not mention pouchitis. Contrary to the Office's assertions, it is clear that treatments for UC or CD are not interchangeable with those for pouchitis, regardless of their shared symptoms and elevated levels of ICAM-1. Thus, as the results in Example 17 of the instant specification are unexpected in view of the cited references, and a *prima facie* case of obviousness was not made by the Office, the pending claims are patentable over the cited references.

Accordingly, for the reasons given above, Applicants request reconsideration of the rejection of the pending claims under 35 U.S.C. § 103(a) over the cited references.

Double Patenting

All pending claims are rejected under the doctrine of nonstatutory obviousness-type double patenting over claims 1-2 and 4-9 of copending Application No. 11/720,745. The Examiner asserts that although the conflicting claims are not identical, they are not patentably distinct from each other.

Applicants respectfully request the Examiner continue to hold the obviousness-type double patenting rejection in abeyance until the present application is otherwise in condition for allowance.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Patents and Applications

Applicants wish to draw the Examiner's attention to the following patents and/or applications. Applicants encourage the Examiner to review and monitor the prosecution of the following patents and/or applications, including all Office Actions, throughout the pendency of this application.

Patent / Serial Number	**Title**	**Issued / Filed**
10/793,497	COMPOSITIONS AND METHODS FOR NON-PARENTAL DELIVERY OF OLIGONUCLEOTIDES	03.04.2004
6,747,014	COMPOSITIONS AND METHODS FOR NON-PARENTAL DELIVERY OF OLIGONUCLEOTIDES	06.08.2004
09/315,298	COMPOSITIONS AND METHODS FOR NON-PARENTAL DELIVERY OF OLIGONUCLEOTIDES	05.20.1999
11/237,063	COMPOSITIONS AND METHODS FOR NON-PARENTAL DELIVERY OF OLIGONUCLEOTIDES	09.28.2005
6,169,079	OLIGONUCLEOTIDE INHIBITION OF CELL ADHESION	01.02.2001
6,300,491	OLIGONUCLEOTIDE INHIBITION OF CELL ADHESION	10.09.2001
09/659,288	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	09.12.2000
6,093,811	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	07.25.2000
6,015,894	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	01.18.2000
5,843,738	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	12.01.1998
6,096,722	ANTISENSE MODULATION OF CELL ADHESION MOLECULE EXPRESSION AND TREATMENT OF CELL ADHESION MOLECULE-ASSOCIATED DISEASES	08.01.2000
6,111,094	ENHANCED ANTISENSE MODULATION OF ICAM-1	08.29.2000
10/454,663	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	06.04.2003
6,849,612	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	02.01.2005
6,887,906	COMPOSITIONS AND METHODS FOR THE DELIVERY OF OLIGONUCLEOTIDES VIA THE ALIMENTARY CANAL	05.03.2005

08/886,829	COMPOSITIONS AND METHODS FOR THE DELIVERY OF OLIGONUCLEOTIDES VIA THE ALIMENTARY CANAL	07.01.1997
07/939,855	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	09.02.1992
5,591,623	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	01.07.1997
5,514,788	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	05.07.1996
5,883,082	COMPOSITIONS AND METHODS FOR PREVENTING AND TREATING ALLOGRAFT REJECTION	03.16.1999
07/567,286	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	08.14.1990
10/559,401	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	N/A
09/659,288	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	09.12.2000
09/082,624	COMPOSITIONS AND METHODS FOR NON-PARENTAL DELIVERY OF OLIGONUCLEOTIDES	05.21.1998

CONCLUSION

Applicants submit that the present application is in condition for allowance and respectfully requests an action to that effect. If any issues remain, the Examiner is invited to contact Applicants' counsel at the number provided below in order to resolve such issues promptly. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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